

AF/60016 HA

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
(Atty Docket No. 104385.140)

In Re:
Application of: Bennett et al.

RECEIVED

Group Art Unit: 1644

Serial Number: 08/722,659

FEB 08 1999

Examiner: Lubet, M.

Filed: September 27, 1996

OFFICE OF PETITIONS
A/C PATENTS

For: USE OF HEPARINASE TO DECREASE INFLAMMATORY RESPONSES

#13
J.S.J.
1/12/99

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to BOX AFTER FINAL Assistant Commissioner for Patents, Washington, D.C. 20231 on the date set forth below.

1/5/99
Date of Signature
and of Mail Deposit

By Patricia Parvey
Patricia Parvey

PETITION UNDER 37 C.F.R. § 1.47(a)

BOX AFTER FINAL
Assistant Commissioner for Patents
Washington, D.C. 20231

RECEIVED
99 JAN 12 AM 8:30
GROUP 180

Sir:

06/15/1999 KPETERSD 00000004 080219 08722659

01 FC:122

130.00 CH

The assignee of this invention, IBEX Technologies Corporation, respectfully petitions the Commissioner under 37 C.F.R. § 1.47(a) to accept the Declaration Pursuant to 37 CFR 1.131 filed on November 23, 1998 in the above-referenced

06/15/1999 KPETERSD 00000002 080219 08722659

Sale Ref: 00000001 080219 08722659

01 FC:122

130.00 CH

Application even though one joint inventor, D. Clark Bennett, has refused to sign the declaration.

This Petition is accompanied by the following:

1. A Declaration of Dr. Richard Vickers with Exhibits A to F.

The Commissioner is hereby authorized to charge the petition fee required under § 1.17(i) to deposit account No. 08-0219.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
(Atty Docket No. 104385.140)

In Re:

Application of: Bennett et al.

Serial Number: 08/722,659

Filed: September 27, 1996



Group Art Unit: 1644

Examiner: Lubet, M.

For: USE OF HEPARINASE TO DECREASE INFLAMMATORY RESPONSES

DECLARATION OF RICHARD S. VICKERS PH.D.

Sir:

The undersigned, Richard S. Vickers, Ph.D., declares and states that:

1. I am the Vice President for Business Development for IBEX Technologies Corporation ("IBEX").
2. Dr. Bennett was employed by IBEX at the time the above-referenced application was filed on September 27, 1996.
3. On or about March 24, 1997, Dr. Bennett's employment with IBEX was terminated.
4. On April 1, 1997, Dr. Bennett executed a Combined Declaration and Power of Attorney and an Assignment which assigned his entire right title and interest in the application to IBEX.
5. I am making this declaration based on first-hand knowledge of the facts surrounding the refusal of one of the joint inventors, D. Clark Bennett, Ph.D., to sign the Declaration Pursuant to 37 CFR 1.131 (the "Declaration") which was filed in the above-referenced application on November 23, 1998.
6. Exhibit A is a copy of the Declaration executed by all joint inventors other than Dr. Bennett.

7. Exhibit B is a copy of a letter dated November 2, 1998 from Ms. Claire Bergeron of IBEX's Montreal Office to Dr. Bennett requesting that he execute the Declaration for the above-referenced application.
8. Exhibit C is a copy of the reply from Dr. Bennett received November 4, 1998 by Ms. Bergeron and forwarded to me. In Dr. Bennett's reply, he states among other things that he believes that the work referred to in the Declaration was completed prior to the publication dates of the listed references, but that, as he does not have personal access to the notebooks from which the exhibits to the Declaration came, he is unwilling to sign the Declaration.
9. On November 4, 1998 I personally spoke to Dr. Bennett by telephone and discussed the Declaration and the exhibits to the Declaration. Based on this conversation, it was my understanding that Dr. Bennett agreed to execute the Declaration.
10. Exhibit D is a copy of my letter dated November 4, 1998 to Dr. Bennett with which I enclosed copies of the notebook pages used as exhibits for the Declaration and a copy of page from his notebook, which page had an earlier date than the notebook pages which were used as exhibits for the Declaration and which page described the concept of the invention. In this letter I referred to my conversation with Dr. Bennett of that morning and restated that the purpose of the Declaration was to "swear behind" the publication dates of the articles cited by the Examiner for the above-referenced application. The dates of the notebook pages have been redacted from this letter. On the same day as this letter was mailed, a new copy of the Declaration and its exhibits were re-sent to him from IBEX's Montreal Office.
11. On November 12, 1998 I attempted to contact Dr. Bennett and was unsuccessful at reaching him personally, so I left a message inquiring if he had any further questions, and asking when I would receive the executed Declaration.

12. On November 13, 1998 I spoke with Dr. Bennett by telephone and discussed the Declaration and the notebook pages which had been provided to him. Dr. Bennett demanded that paragraph 5 of the Declaration be amended to insert "I believe that" at the beginning of the first sentence, such that the sentence would now read "I believe that prior to the publication dates of the articles cited in paragraph 2 above, we conceived of and reduced to practice the invention which is most broadly claimed in Claim 1 of the above-referenced patent application." Dr. Bennett also demanded that he be provided with the original notebooks to verify the dates on the pages. I explained that IBEX could not send the original notebooks to him and offered that notarized copies of the notebook pages which are used as exhibits to the Declaration and notarized copies of his relevant notebook pages be sent to him instead. Based on this conversation, it was my understanding that Dr. Bennett agreed to execute the Declaration if it was amended as above and if he was provided with notarized copies of the relevant notebook pages.

13. Exhibit E is a copy of the Declaration that was amended as requested by Dr. Bennett (hereafter the "Bennett Declaration").

14. Exhibit F is a copy of my letter dated November 17, 1998 to Dr. Bennett with which I enclosed the Bennett Declaration and notarized copies of the relevant notebook pages.

15. On each of December 1, 1998 and December 4, 1998, I telephoned Dr. Bennett to inquire when he would return the executed Bennett Declaration. Each time I was unable to reach Dr. Bennett personally and left him a message on his personal voicemail.

16. On December 8, 1998, I spoke with Dr. Bennett by telephone. In that conversation Dr. Bennett stated that he refused to execute the Bennett Declaration and that he would not execute any documents for IBEX in the future.

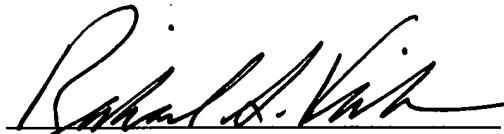
17. On information and belief, Dr. Bennett has not signed the Declaration Pursuant to 37 CFR 1.131 for the above-referenced patent application.

18. On information and belief, filing of the Declaration Pursuant to 37 CFR 1.131 under 37 CFR §1.47(a) is necessary to preserve the rights of the assignee, IBEX Technologies Corporation.

19. I declare further that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true, and further that the statements are made with the knowledge that wilful false statements and the like are punishable by fine or imprisonment, or both, under §1001 of Title 18 of the United States Code, and that such wilful false statements may jeopardize the validity of the patent application or any patent issuing thereon.

Respectfully submitted,

Dated: December 21, 1998

A handwritten signature in black ink, appearing to read "Richard S. Vickers", written over a horizontal line.

Richard. S. Vickers, Ph.D.
Vice President for Business Development
IBEX Technologies Corporation

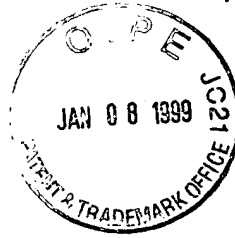
IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
(Atty Docket No. 104385.140)

In Re:

Application of: Bennett et al.

Serial Number: 08/722,659

Filed: September 27, 1996



Group Art Unit: 1644

Examiner: Lubet, M.

For: USE OF HEPARINASE TO DECREASE INFLAMMATORY RESPONSES

DECLARATION PURSUANT TO 37 C.F.R. §1.131

We, D. Clark Bennett, Elizabeth Cauchon, Ariane Hsia, Pamela Danagher, Brigitte Grouix and Joseph Zimmermann, hereby declare as follows:

1. We are the co-inventors of the above-referenced patent application, which claims priority to provisional application 60/004,622, filed September 29, 1995.
2. We understand that this Declaration is being made to establish a date of invention prior to the date of publication for the following publications which have been cited against the above-referenced patent application by the Examiner:
3. Each of the listed publications was published less than one year prior to the priority date of the instant application.
 - a. Gilat et al., (1995) J. Exp. Med., vol. 181, pp. 1929-1934, published May 1995.
 - b. Gilat et al., (1994) J. Immunol. vol. 153, pp 4899-4906, published December 31, 1994
 - c. Hoogewerf et al., (1995) J. Biol. Chem., vol. 270, pp. 3268-3277, published February 17, 1995.
 - d. Lider et al., (1995) Proc. Natl. Acad. Sci. USA, vol. 92, pp. 5037-5041, published May 1995.

Serial Number: 08/722,659
Group Art Unit: 1816
Examiner: M. Lubet
Page 2

4. The invention was conceived and reduced to practice in a NAFTA country, Canada, and is entitled to the provisions 35 USC § 104.

5. Prior to the publication dates of the articles recited in paragraph 2 above, we conceived of and reduced to practice the invention which is most broadly claimed in Claim 1 of the above-referenced patent application.

6. Attached hereto as EXHIBIT A, Pages 14 and 15, are true copies of laboratory notebook pages from a bound laboratory notebook, signed by Elizabeth Cauchon and witnessed by Pamela Danagher, except that the dates on the pages have been removed. The redacted dates are all prior to each of the publication dates listed in paragraph 2 above.

7. Notebook Pages 14 and 15 are a record of the reduction to practice of the invention in an *in vitro* neutrophil transmigration assay system. This assay system is an accepted *in vitro* model of neutrophil extravasation and is used to analyze conditions affecting neutrophil extravasation, a key step in local inflammatory response. The results presented in Notebook Pages 14 and 15 demonstrated that heparinase treatment of HUVECs (human umbilical venous endothelial cells) inhibits neutrophil transmigration. The demonstrated inhibition of *in vitro* neutrophil transmigration reasonably infers that a localized inflammatory response in tissue can be decreased by administration of heparinase enzyme to a patient. The results of several neutrophil transmigration assays were presented in the provisional application on pages 26-29 (Example 4).

9. We hereby further declare that all statements made herein of our own knowledge are true and that all statements made on information and belief are believed to be true and further that these statements were made with the knowledge

Serial Number: 08/722,659

Group Art Unit: 1816

Examiner: M. Lubet

Page 3

that willful false statements and the like so made are punishable by fine or imprisonment or both under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Signed: _____
D. Clark Bennett

Dated: _____

Signed: Elizabeth Cauchon
Elizabeth Cauchon

Dated: November 2, 1998

Signed: _____
Ariane Hsia

Dated: _____

Signed: _____
Pamela Danagher

Dated: _____

Signed: _____
Brigitte Grouix

Dated: _____

Signed: _____
Joseph Zimmermann

Dated: _____

Serial Number: 08/722,659
Group Art Unit: 1816
Examiner: M. Lubet
Page 3

that willful false statements and the like so made are punishable by fine or imprisonment or both under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Signed: _____
D. Clark Bennett

Dated: _____

Signed: _____
Elizabeth Cauchon

Dated: _____

Signed: *Ariane Hsia*
Ariane Hsia

Dated: *Nov. 8, 1998*

Signed: _____
Pamela Danagher

Dated: _____

Signed: _____
Brigitte Grouix

Dated: _____

Signed: _____
Joseph Zimmermann

Dated: _____

Serial Number: 08/722,659
Group Art Unit: 1816
Examiner: M. Lubet
Page 3

that willful false statements and the like so made are punishable by fine or imprisonment or both under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Signed: _____
D. Clark Bennett

Dated: _____

Signed: _____
Elizabeth Cauchon

Dated: _____

Signed: _____
Ariane Hsia

Dated: _____

Signed: 
Pamela Danagher

Dated: November 12, 1998

Signed: _____
Brigitte Grouix

Dated: _____

Signed: _____
Joseph Zimmermann

Dated: _____

Serial Number: 08/722,659
Group Art Unit: 1816
Examiner: M. Lubet
Page 3

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Signed: _____
D. Clark Bennett

Dated: _____

Signed: _____
Elizabeth Cauchon

Dated: _____

Signed: _____
Ariane Hsia

Dated: _____

Signed: _____
Pamela Danagher

Dated: _____

Signed: _____
Briette Grouix

Dated: 4-11-98

Signed: _____
Joseph Zimmermann

Dated: _____

Serial Number: 08/722,659
Group Art Unit: 1816
Examiner: M. Lubet
Page 3

that willful false statements and the like so made are punishable by fine or imprisonment or both under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Signed: _____
D. Clark Bennett

Dated: _____

Signed: _____
Elizabeth Cauchon

Dated: _____

Signed: _____
Ariane Hsia

Dated: _____

Signed: _____
Pamela Danagher

Dated: _____

Signed: _____
Brigitte Grouix

Dated: _____

Signed: _____
Joseph Zimmermann

Dated: _____
Nov 5, 1998

EXHIBIT A

- one plate of HUVEC P7 was trypsinised and 2×10^5 cells were plated per insert (8mm, coated with fibronectin), 29 inserts total. The media was changed every day until they reached complete confluency.

Neutrophil migration assay

Neutrophils migrate in response to a gradient of IL-8. IL-1 stimulated HUVEC cells will produce IL-8 at their cell surface where it presumably binds to heparin. By digesting heparin with our heparinase 3, the IL-8 will diffuse in media and neutrophils, who follow the gradient, will not be attracted to the cell surface, preventing them from migrating into the wells.

One filter on which HUVEC cells were growing was stained with crystal violet (see protocol on page 6). The cells were confluent. Media was taken out of the wells and IL-1 (2 ng/ml) was added to 18 wells. The others received culture media only. After 4 hours, the wells were emptied again, along with the inserts and Hep 3 at 110 ng/ml in PBS was added to both the wells and the inserts, to 9 of them. The others received PBS only. The digestion was allowed to proceed for one hour at 37°C. One insert that received hep 3 was then stained to see if the cells had detached and it appeared that some had in fact lifted. A different coating is going to be tried next time.

All the inserts were emptied (along with the wells) and 0.3 ml of culture media was added to them. The wells and inserts that had some Hep 3 received culture media without heparin (RPMI + 20% FS). 1.5×10^6 neutrophils were added to every insert and their migration was

Continued on Page 15

Read and Understood By

Elizabeth Cauchon

Signed

Date

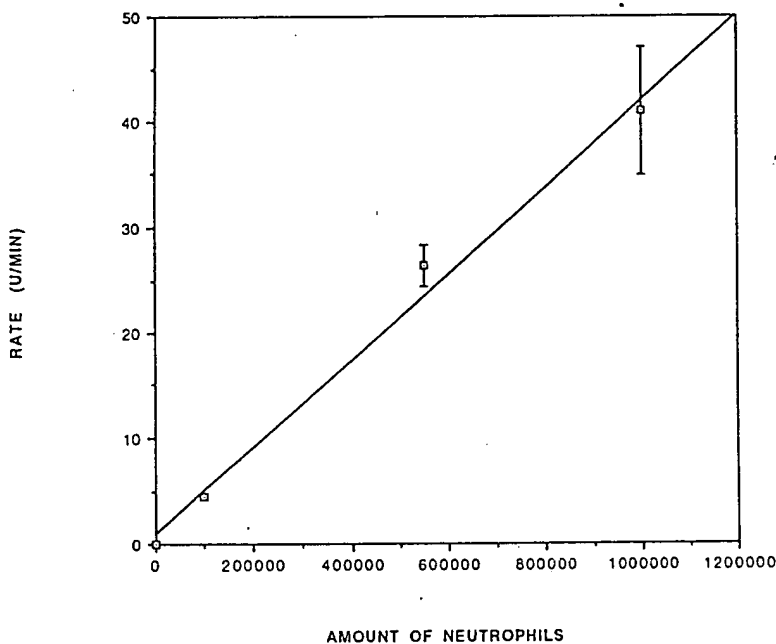
Lamela Hargreaves

Signed

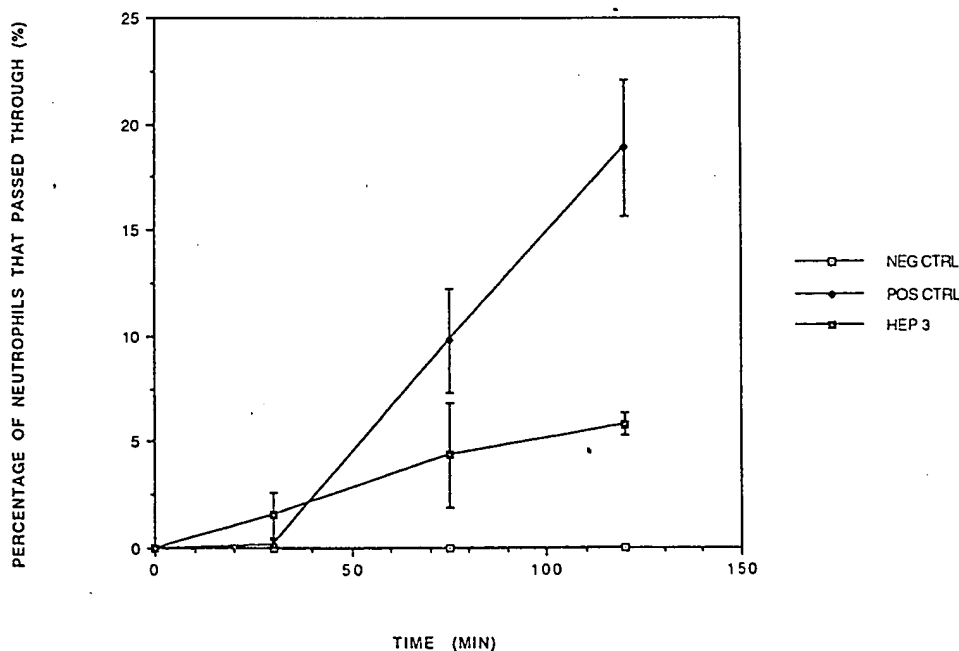
Date

stopped at 1/2 hr, 1 1/4 hr and 2 hours by taking out the inserts (3 filters of each series per time point). The bottom of the inserts were rinsed and the rinse was added to the content of the well. The samples were kept at -20°C o/n. and a myeloperoxidase assay was done the day after.

MYELOPEROXIDASE ASSAY OF HUMAN NEUTROPHILS



MIGRATION OF NEUTROPHILS THROUGH A LAYER OF HUVEC CELLS DIGESTED WITH HEP 3 AT 1 IU/ML FOR AN HOUR



Raw Data
In Raw
Data Binder
p. 1 to 9

ued on Page 16

Read and Understood By

Elizabeth Caudon

Ramona Doughty

Date

Signed

Date

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
(Atty Docket No. 104385.140)

In Re:

Application of: Bennett et al.

Group Art Unit: 1644

Serial Number: 08/722,659

Examiner: Lubet, M.

Filed: September 27, 1996

For: USE OF HEPARINASE TO DECREASE INFLAMMATORY RESPONSES

EXHIBIT A

EXHIBIT A

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One filter on which HUVEC cells were growing was stained with crystal violet (see protocol on page 6). The cells were confluent. Media was taken out of the wells and IL-1 (2 ng/ml) was added to 18 wells. The others received culture media only. After 4 hours, the wells were emptied again, along with the inserts and Hep 3 at 110 ng/ml in PBS was added to both the wells and the inserts, to 9 of them. The others received PBS only. The digestion was allowed to proceed for one hour at 37°C. One insert that received Hep 3 was then stained to see if the cells had detached and it appeared that some had in fact lifted. A different coating is going to be tried next time.

All the inserts were emptied (along with the wells) and 0.5 ml of culture media was added to them. The wells and inserts that had some Hep 3 received culture media without heparin (RPMI + 20% FS). 1.5×10^6 neutrophils were added to every insert and their migration was

Continued on Page 15

Read and Understood By

Elizabeth Cauchon

Signed

Date

Lamela Humph

Signed

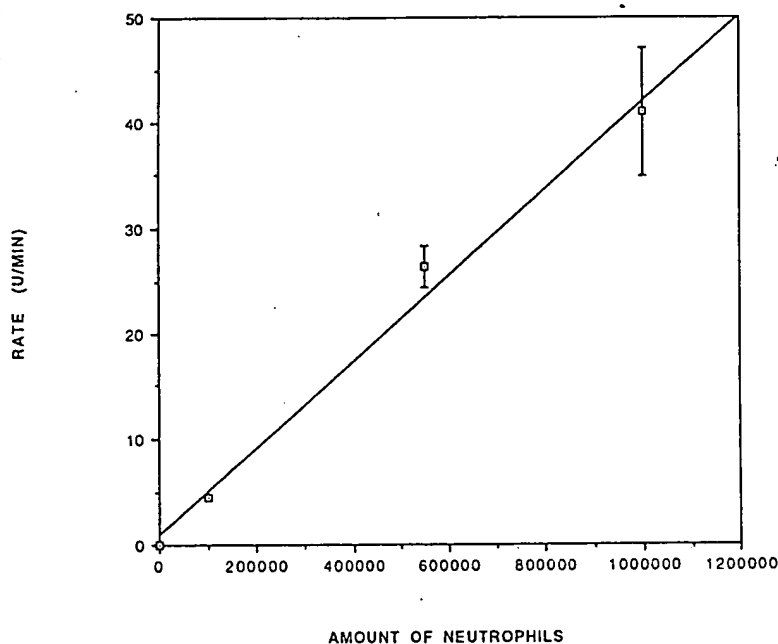
Date

PROJECT _____

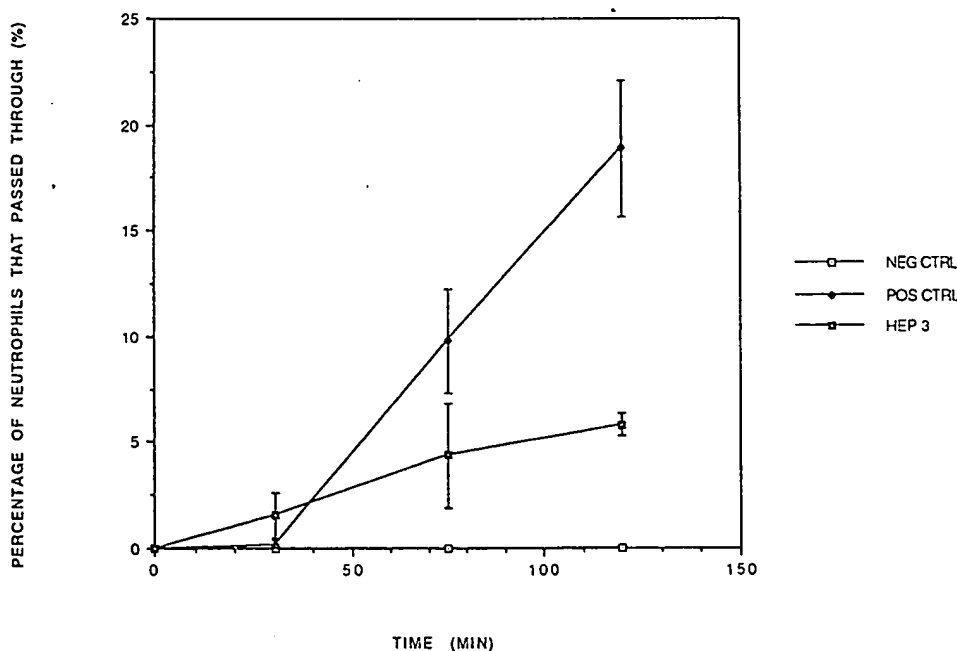
Continued From Page 14

stopped at 1/2 hr, 1 1/4 hr and 2 hours by taking out the inserts (3 filters of each series per time point). The bottom of the inserts were rinsed and the rinse was added to the content of the well. The samples were kept at -20°C o/n. and a myeloperoxidase assay was done the day after.

MYELOPEROXIDASE ASSAY OF HUMAN NEUTROPHILS



MIGRATION OF NEUTROPHILS THROUGH A LAYER OF HUVEC CELLS DIGESTED WITH HEP 3 AT 1 IU/ML FOR AN HOUR



Raw Data
In Raw
Data Binder
p. 1 to 9

ued on Page 16

Read and Understood By

Elizabeth Caudon
Signed

Ramona Doughty
Signed

Date

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
(Atty Docket No. 104385.140)

In Re:

Application of: Bennett et al.

Group Art Unit: 1644

Serial Number: 08/722,659

Examiner: Lubet, M.

Filed: September 27, 1996

For: USE OF HEPARINASE TO DECREASE INFLAMMATORY RESPONSES

EXHIBIT B

IBEX

November 2, 1998

IBEX Technologies Inc.
5485 Paré, Montréal, Québec, Canada H4P 1P7
Tél.: (514) 344-4004 • Fax: (514) 344-8827
Email: Info@IBEX.ca

VIA FEDERAL EXPRESS

Clark Bennett
1687 Sunnycove Drive
Mississauga, Ontario
L4X 1B6

Re: U.S. Patent Application Serial No. 08/722,659 for
"Use of Heparinases to Decrease Inflammatory Responses"


Dear Mr. Bennett:

Your assistance is needed in formulating a response to the patent Examiner handling the above-noted application. Several published articles have been cited by the Examiner as prior art against this application. Since all of these articles were published AFTER the date on which this invention was made and reduced to practice, they can be eliminated as prior art by "swearing behind" or formally declaring this to be fact.

Enclosed is a formal Declaration prepared by our patent attorney for this purpose. I ask that you carefully read the Declaration, the pending claims, and Example 4 from the pending application. If the representations are factually correct, please sign and return the Declaration using the enclosed pre-addressed/direct-billed Fed-Ex envelope by Friday, November 13th

Please accept my appreciation in advance for your cooperation in this matter.

Sincerely,


Claire Bergeron
Manager, Administrative Services

CB/df
Enclosure

See Back!

*See Corrections to
Text*

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
(Atty Docket No. 104385.140)

In Re:

Application of: Bennett et al.

Group Art Unit: 1644

Serial Number: 08/722,659

Examiner: Lubet, M.

Filed: September 27, 1996

For: USE OF HEPARINASE TO DECREASE INFLAMMATORY RESPONSES

EXHIBIT C

Claire;

To the best of my ~~own~~ knowledge the work was done before the dates of the listed publications.

Because I no longer have access to my notebooks or the notebooks of others, I cannot sign this because of statement #5 or the second line in statement #6. I do not know that either of these statements are true. The proof ^{you need} should be in the notebooks if you would know where to look.

D. Clark Bennett

P.S. Sorry for the handwriting. My computer is packed,

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
(Atty Docket No. 104385.140)

In Re:

Application of: Bennett et al.

Group Art Unit: 1644

Serial Number: 08/722,659

Examiner: Lubet, M.

Filed: September 27, 1996

For: USE OF HEPARINASE TO DECREASE INFLAMMATORY RESPONSES

EXHIBIT D

IBEX

November 4, 1998

VIA EXPRESS MAILIBEX Technologies Corporation
5 Great Valley Parkway, Suite 300, Malvern, PA 19355
Tel.: (610) 407-4200 • Fax: (610) 407-4270D. Clark Bennett, Ph.D.
1687 Sunnycove Drive
Mississauga, Ontario L4X 1B6
CANADA

Dear Clark:

Thank you for your willingness to re-consider signing the Declaration for the patent application dealing with "Use of Heparinase to Decrease Inflammatory Responses." The original packet of information and Declaration are being re-sent to you from Montreal. It should arrive at the same time that this letter is received.

Enclosed are copies of Research Notebook pages which we discussed this morning:

- Page 28 of your Notebook No. 029405 (dated _____ and witnessed _____) in which the concept of heparinase treatment to remove endothelial membrane heparin and breakdown the chemokine concentration gradient is described; and
- Page 14 and 15 of Elizabeth Cauchon's Notebook No. 029402 (dated _____ and witnessed _____) in which the reduction to practice of heparinase treatment to remove binding sites for chemokines and reduce neutrophil migration is described.

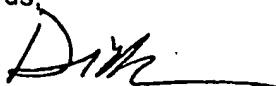
The latter pages describing the reduction to practice of the invention were used in the Declaration. Please note that both the dates of conception and reduction to practice are earlier than any dates of publication for the cited articles (December, 1994 - May, 1995).

As noted previously, the purpose of this Declaration is to "swear behind" the publication dates of the articles cited by the Patent Examiner as prior art. Having copies of these notebook pages with dates included, you should now be able to sign Articles 5 and 6 of the Declaration with a clear conscience.

Please accept my appreciation in advance for signing and returning the Declaration.

Good luck with your move. I am sure that you and your family will enjoy Connecticut! I am familiar with the area having lived in North Branford (near New Haven) for several years.

Best regards,



Richard S. Vickers, Ph.D.

Enclosures

cc: R. Heft, Ph.D.
G. Rice, Ph.D. (Hale & Dorr) *via FAX 4-111*

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
(Atty Docket No. 104385.140)

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Application of: Bennett et al.

Group Art Unit: 1644

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EXHIBIT E

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
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DECLARATION PURSUANT TO 37 C.F.R. §1.131

We, D. Clark Bennett, Elizabeth Cauchon, Ariane Hsia, Pamela Danagher, Brigitte Grouix and Joseph Zimmermann, hereby declare as follows:

1. We are the co-inventors of the above-referenced patent application, which claims priority to provisional application 60/004,622, filed September 29, 1995.
2. We understand that this Declaration is being made to establish a date of invention prior to the date of publication for the following publications which have been cited against the above-referenced patent application by the Examiner:
3. Each of the listed publications was published less than one year prior to the priority date of the instant application.
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 - b. Gilat et al., (1994) J. Immunol. vol. 153, pp 4899-4906, published December 31, 1994
 - c. Hoogewerf et al., (1995) J. Biol. Chem., vol. 270, pp. 3268-3277, published February 17, 1995.
 - d. Lider et al., (1995) Proc. Natl. Acad. Sci. USA, vol. 92, pp. 5037-5041, published May 1995.

Serial Number: 08/722,659

Group Art Unit: 1816

Examiner: M. Lubet

Page 2

4. The invention was conceived and reduced to practice in a NAFTA country, Canada, and is entitled to the provisions 35 USC § 104.

5. I believe that prior to the publication dates of the articles recited in paragraph 2 above, we conceived of and reduced to practice the invention which is most broadly claimed in Claim 1 of the above-referenced patent application.

6. Attached hereto as EXHIBIT A, Pages 14 and 15, are true copies of laboratory notebook pages from a bound laboratory notebook, signed by Elizabeth Cauchon and witnessed by Pamela Danagher, except that the dates on the pages have been removed. The redacted dates are all prior to each of the publication dates listed in paragraph 2 above.

7. Notebook Pages 14 and 15 are a record of the reduction to practice of the invention in an *in vitro* neutrophil transmigration assay system. This assay system is an accepted *in vitro* model of neutrophil extravasation and is used to analyze conditions affecting neutrophil extravasation, a key step in local inflammatory response. The results presented in Notebook Pages 14 and 15 demonstrated that heparinase treatment of HUVECs (human umbilical venous endothelial cells) inhibits neutrophil transmigration. The demonstrated inhibition of *in vitro* neutrophil transmigration reasonably infers that a localized inflammatory response in tissue can be decreased by administration of heparinase enzyme to a patient. The results of several neutrophil transmigration assays were presented in the provisional application on pages 26-29 (Example 4).

9. We hereby further declare that all statements made herein of our own knowledge are true and that all statements made on information and belief are believed to be true and further that these statements were made with the knowledge

Serial Number: 08/722,659

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Page 3

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Signed:

D. Clark Bennett

Dated:

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
(Atty Docket No. 104385.140)

In Re:

Application of: Bennett et al.

Group Art Unit: 1644

Serial Number: 08/722,659

Examiner: Lubet, M.

Filed: September 27, 1996

For: USE OF HEPARINASE TO DECREASE INFLAMMATORY RESPONSES

EXHIBIT F

IBEX

November 17, 1998

VIA EXPRESS MAILIBEX Technologies Corporation
5 Great Valley Parkway, Suite 300, Malvern, PA 19355
Tel.: (610) 407-4200 • Fax: (610) 407-4270D. Clark Bennett, Ph.D.
241 Trumbull Road
Waterford, CT 06385

Dear Clark:

Enclosed is a revised Declaration for the patent application dealing with "Use of Heparinase to Decrease Inflammatory Responses." I have included the original page along with a "mark-up" showing the revision.

Since we cannot send you the original Research Notebooks and it is impractical for you to travel to Montréal to personally look at them, I have enclosed notarized copies of the relevant pages:

- Page 28 of your Notebook No. 029405 (dated _____ and witnessed _____) in which the concept of heparinase treatment to remove endothelial membrane heparin and breakdown the chemokine concentration gradient is described; and
- Pages 14 and 15 of Elizabeth Cauchon's Notebook No. 029402 (dated _____ and witnessed _____) in which the reduction to practice of heparinase treatment to remove binding sites for chemokines and reduce neutrophil migration is described.

As noted previously, only the latter pages describing the reduction to practice of the invention have been used for the Declaration.

Since the purpose of this Declaration is to "swear behind" the publication dates of the articles cited by the Patent Examiner as prior art, it is only necessary that the invention pre-date the publications by one day. The notarized pages containing the dates of conception and reduction to practice of the invention show that both events occurred at least four months prior to the publication dates for the cited articles (December 31, 1994 - May, 1995).

Having revised the text of the Declaration per your request and having provided certified copies of the cited Research Notebook pages, I ask that you now sign, date and return the Declaration to me at your earliest convenience. I have enclosed an addressed, pre-paid express mail envelope for this purpose.

Sincerely,



Richard S. Vickers, Ph.D.

Enclosures

cc: R. Heft, Ph.D.
G. Rice, Ph.D. (Hale & Dorr)